REMARKS

Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 1-3, 12, 14-33 and 42-44 are pending. Claims 4, 11 and 13 are cancelled without prejudice or disclaimer. Claims 1, 14, 15, 22-24, 27, 30 and 42-44 are amended. Claim 1 is amended to incorporate the limitations of claim 13 and for clarity as suggested by the Examiner. Claims 22-24, 27 and 30 are similarly amended, and claims 14, 15 and 42 are amended to properly depend from base claims. The amendments render it clear that the in the claimed methods, sets of nucleic acids encoding proteins that differ in one amino acid from the target protein are prepared, the sets are individually expressed and screened to identify modified proteins that have a predetermined activity. As noted previously, the methods involve modifying nucleic acid molecules one codon at a time to replace a single amino acid at a time, introducing modified nucleic acid molecules one-by-one into host cells and individually screening each protein that is produced so that each modified protein is expressed and screened separately. This is as described in the application. For example, in the first paragraph of the "Summary," the application states:

> In practicing the methods, each molecule is individually designed, produced, processed, screened and tested in a high throughput format. Neither random or combinatorial methods nor mixtures of molecules are used.

This description is repeated throughout the application; although in the first step, the application describes that the molecules are not necessarily individually designed, but can be prepared by any method. Once designed, molecules, such as nucleic acid molecules are individually expressed, screened and tested. To advance prosecution, the first step of the method is now directed to the embodiments in which the sets nucleic acid molecules are rationally designed and the members of each set encode proteins that only differ from the target protein and members of each other set by one amino acid. No new matter is added.

CLAIM OBJECTIONS

Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Cancellation of claim 4 herein renders this ground for rejection moot.

THE REJECTIONS OF CLAIMS 1-21 AND 42-44 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-21, and 42-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for reasons addressed in turn below for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. This rejection is respectfully traversed.

Claim 1 is rejected in the recitation of "the host cells are provided as an addressable array" because it is unclear in that "it seems to state that the cells themselves are an addressable array, rather than the cells are found in an addressable array or the cells are organized in an addressable array."

Claims 1, 22-24 and 27 are amended to recite that the cells are **organized in** an addressable array as suggested by the Examiner. It is emphasized that such amendment is not intended to limit the meaning of array nor an addressable array. As described in the specification, an addressable array does not necessarily refer to a solid matrix upon which or in which cells or other moieties are localized. As described in the application, an array is a collection of elements, immobilized or not immobilized; and an addressable array is one in which loci thereof can be identified. Such loci and identification is not required to be a positional localization, but can be identifiable by encoding constituents of the collection. See, for example, page 27, line 20, - page 28, line 2:

> As used herein, an array refers to a collection of elements, such as nucleic acid molecules, containing three or more members. An addressable array is one in which the members of the array are identifiable, typically by position on a solid phase support or by virtue of an identifiable or detectable label, such as by color, fluorescence, electronic signal (i.e. radiofrequency (RF), microwave or other frequency that does not substantially alter the interaction of the molecules of interest), bar code or other symbology, chemical or other such label. Hence, in general the members of the array are immobilized to discrete identifiable loci on the surface of a solid phase or directly or indirectly linked to or otherwise associated with the identifiable label, such as affixed to a microsphere or other particulate support (herein referred to as beads) and suspended in solution or spread out on a surface.

For example, the cells can be labeled for identified, such as by color coding, chemical labeling, RF tagging, or can be deposited on a matrix at positionally addressable loci. Amending the claim as suggested by the Examiner excludes such embodiments, and, hence is unduly limiting. The language recited in the claims does not exclude such alternative embodiments. Hence, by reciting that the cells are provided as an addressable array, the

means that the cells are provided as a collection with identifiable loci. The amendment herein to recite that the cells are organized in an addressable array is not intended to alter that meaning.

Claims 14, 15, 43 and 44 are indefinite in the recitation "the codon" because the antecedent in the parent is unclear. Amendment of the claims to recite "pre-selected codon" to clarify that it is the replacing codon obviates this rejection.

THE REJECTION OF CLAIMS 1-6, 8-23, 30, 32, 33 AND 42-44 UNDER 35 U.S.C. §102(b)

Claims 1-6, 8-23, 30, 32, 33, and 42-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Giver *et al.* ((1988) *Proc. Natl. Acad. Sci. U.S.A 95*:12809-12813) because it is alleged that:

> [t]he instant claims are drawn to a method of identifying proteins with different properties by producing a set of nucleic acid molecules that encode modified proteins that differ from a target protein by one amino acid; introducing the nucleic acids into host cells on a array; expressing the proteins; screening the proteins for a chemical, physical, or biological property that differs from the target protein; and designating proteins with a different property from the target protein as a hit.

The Examiner urges that Giver *et al.*. discloses:

> a method of producing sets of nucleic acids that encode for proteins that differ from the target protein by one amino acid (page 12809, right column, under Materials and Methods); introducing the nucleic acids into host cells (page 12810, left column, top paragraph) which were then placed into an addressable array (96 well plates) wherein each well had the same modified nucleic acid molecule (page 12810, left column top paragraph); expressing the proteins which differ from the target protein and modified proteins by one amino acid (page 12809, right column, under Materials and Methods; page 12810, left column); screening the proteins for a chemical, physical or biological property (page 12810); designating each protein and its mutation with a different property as a hit (page 12810-12811; page 12812, left column bottom).

The Examiner sets forth further arguments with respect to elements in dependent claims (contradicting rejections set forth under 35 U.S.C. §103(a) below). Because the rejection is flawed with respect to claim 1 and other independent claims, it is not necessary to reach the merits of the dependent claims. This rejection is respectfully traversed. It is respectfully submitted that the Examiner has (1) mischaracterized the claimed methods; and (2) mischaracterized the disclosure of cited reference. It is noted that silence with respect to the merits of the rejection of dependent claims is **not** to be construed as acquiescence, but

reflects the fact that Giver *et al.* fails to disclose the elements of the independent claims. Accordingly, it cannot disclose all elements of any dependent claim, which by definition include all limitations of a base claim.

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). A reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE REJECTED CLAIMS

Independent claim 1 is directed to a process for the identification of a protein that differs in a predetermined property from a target protein, comprising:

> (a) producing separate sets of nucleic acid molecules that encode modified forms of a target protein, wherein:
>
> the nucleic acid molecules in each set are produced by changing one codon in the target protein to a pre-selected codon, whereby the nucleic acid molecules in each set encode proteins that differ from the encoded proteins in another set by one amino acid; and
>
> all nucleic acid molecules in a set encode the same modified protein;
>
> (b) individually introducing each set of nucleic acid molecules into host cells, wherein:
>
> the host cells are provided as an addressable array; and
>
> the cells of each locus of the addressable array contain the same modified nucleic acid molecule;
>
> (c) expressing the encoded proteins, whereby sets of proteins encoded by the nucleic acid molecules are produced, wherein:

all of the encoded proteins in each set have the same modification; and

the proteins in each set differ from the proteins in another set by one amino acid and from the target protein by one amino acid; and

(d) individually screening each set of encoded proteins, whereby one or more proteins that have a predetermined property that differs from the target protein is/are identified, wherein:

each such protein is designated a hit;

each hit contains a mutation designated a hit position; and

the predetermined property is selected from among a chemical, a physical and a biological property of the target protein.

Claim 22 is directed to the process for the identification of a protein that differs in a predetermined property from a target protein by individually expressing proteins that differ by one amino acid and individually screening them. Claim 22 recites that the predetermined property is selected from among a chemical, a physical and a biological property of the target protein, wherein the change in a predetermined property comprises a change in an activity of the target protein that is at least about 10%, 20%, 30%, 40% or 50% compared to the unmodified target protein. Claim 23 recites that the change in the predetermined property comprises a change in an activity of the target protein that is at least about 75%, 100%, 200%, 500% or 1000% compared to the unmodified target protein. Claim 24 and dependent claims recite that the "predetermined property is selected from among a chemical, a physical and a biological property of the target protein". Claim 27 and dependent claims recite that the "nucleic acid molecules comprise viral vectors; and the cells are eukaryotic cells that are transduced with the vectors," and claim 30 and dependents recite that "performance of the screened proteins is evaluated by a Hill analysis or by fitting the output signal to a curve representative of the interaction of the target protein and a test compound."

Hence all of the claims are directed to method of directed evolution in which a target protein is modified one amino acid at a time, and each modified protein is expressed and screened separately from the other modified proteins. One amino acid change is introduced per protein, not one or changes, but one change. Mixtures of different proteins are not produced, nor are mixtures screened. In addition, host cells containing the nucleic acid encoding each protein are addressably arrayed, which means that the identity of the nucleic acid at each locus in the array, and, thus the protein, is known.

As described in the application this method does not rely on any methods in which there is differential modification or expression of a particular modified protein. For example, at page 24, lines 6-24, the specification states:

> The whole process of the 'identification of the active site(s) on the full length protein sequence requires the following sub-steps:
>
> a. Generation of a mutant library (on the gene to be evolved) in which each individual mutant contains a single mutation located at a different amino acid position and that includes a systematic replacement of the native amino acid by Ala or any other amino acid (always the same throughout the entire protein sequence);
>
> b. phenotypic characterization of the individual mutants, one-by-one and assessment of mutant protein activity;
>
> c. identification of those mutants that display an alteration, typically a decrease, in the selected protein activity, thus, indicating that amino acids directly involved in the active site(s) have been hit. The aa positions whose aa-scan mutations display an alteration, typically a loss or decrease, in activity are named HITS.
>
> The identification of the active site(s) (HITS) is thus, by this method, made in a completely unbiased manner. There are no assumptions about the specific structure of the protein in question nor any knowledge or assumptions about the active site(s). The results of the amino acid scan identify such sites.

Hence, there is no bias introduced into the process. Amino acids are rationally replaced and each variant is tested separately. There is no reliance upon differential expression in culture in which conditions could favor one variant over another. Further, as exemplified, the method is quite powerful, permitting evolution, for example, of AAV Rep proteins to produce modified AAV that has that has increased titer. While modifications in the viral Rep genes was known, there had been no mutations identified that result increased titer. The instantly claimed unbiased systematic rational method permitted mutations that result in increased titer to be identified.

The Examiner has mischaracterized the claim

As noted above, the Examiner states that:

> [t]he instant claims are drawn to a method of identifying proteins with different properties by producing a set of nucleic acid molecules that encode modified proteins that differ from a target protein by one amino acid; introducing the nucleic acids into host cells on a array; expressing the proteins; screening the proteins for a chemical, physical, or biological property that differs from the target protein; and designating proteins with a different property from the target protein as a hit.

It respectfully is submitted that this characterization of the claims is incorrect. The instantly claimed methods produce separate sets of nucleic acid molecules. Each set encodes the same protein, and the protein encoded by each set differs from each other set by one amino acid. Hence, the method does not include a step in which mixtures of nucleic acid molecules that encode different proteins are prepared. Further, as claimed, the sets are individually introduced into host cells and each set is expressed to produce one protein at each locus of an array. Each protein is separately screened.

Giver *et al.*

Giver *et al.* discloses a method for evolving a protein to have increased thermal stability without loss of its activity at lower temperature. The method involves the steps of producing nucleic acid molecules encoding variants of an esterase by gene random mutagenesis to produce a mixture of the variants called a random mutant library, screening the expressed gene libraries in *E. coli* to produce colonies, which colonies are picked into 96-well microtiter plates. The process of random mutagenesis followed by screening was repeated six times. Giver *et al.* also states that one or two mutations are introduced per nucleic acid molecules, which are expressed as a mixture.

The method of Giver *et al.* is completely different from the instantly claimed method. It differs in numerous steps. In the instantly claimed methods mutants are rationally produced by mutating one codon at a time to produce sets of nucleic acid molecules that each encode the same protein that differs from the target protein by one amino acid; separately expressing each set and screening the expressed proteins. In the method of Giver *et al.*, the mutated nucleic acids are produced by random mutagenesis, including gene shuffling, all variants are made in the same mixture and are expressed in the mixture, colonies are produced, picked and screened. The colonies may be placed in an array, but they are not addressably arrayed, since each colony is indistinguishable from the next; whereas in the instantly claimed methods the identity of the nucleic acid molecule in the host cell and the encode protein at each locus in the array is known. Hence the method of Giver *et al.* bears no resemblance to the rational methods of the instant claims.

The Examiner points to page 12809, col. 2 to urge that Giver *et al.* discloses a method in which sets of nucleic acid molecules that differ from the target protein by one amino acid are produced. It respectfully is submitted that this is not correct. Givers *et al.* states, page 12809, col. 2, that random mutations were introduced using mixtures of primers: "Random

mutations were introduced during mutagenic PCR (14)." The primers introduce *one to two* amino acid modifications per encoded protein, and the modified nucleic acids are produced as a mixture resulting in sets of nucleic acids that encode mixtures (libraries) of proteins, in which members of the mixtures differ from the target protein by 1-2 amino acids. The sets do not contain nucleic acid molecules that encode the same protein nor do the proteins encoded by each set differ by one amino acid from the proteins in another set.

The Examiner states that the nucleic acid molecules were introduced into cells which were arrayed. It respectfully is submitted that this is not correct. The nucleic acid molecules, which contain mixtures of different proteins were introduced into cells and the cells were grown and colonies were picked and the plates were screened. Hence the proteins were not separately expressed and screened as required by the instantly claimed methods.

Analysis

Giver *et al.* does not disclose a method that includes any or all of the steps (a)-(d), common to all pending claims, as follows.

(a) Producing a population of sets of nucleic acid molecules that encode modified forms of a target protein, where the members of each set encode the ***same*** modified protein, and each encoded modified protein in a set differs from the encoded proteins in each other set and from the target protein by one amino acid

As discussed above, Giver *et al.* employs mixtures of oligonucleotides that in which **one to two** amino acids are modified in each encoded protein to produce mixtures of oligonucleotides.

(b) Individually introducing each set of nucleic acid molecules into host cells, and expressing the encoded protein, where the host cells are organized in an addressable array; the cells of each locus of the addressable array contain the same modified nucleic acid molecule; all proteins in each set contain the same modification; and the proteins in each set differ from the proteins in another set by one amino acid and from the target protein by one amino acid.

In the method of Giver *et al.* the mixtures of nucleic acid molecules are introduced into host cells and are expressed in the host cells. In the instantly claimed method, the same protein is expressed in each set of host cells. Further, in the method of Giver *et al.*, the cells may be arrayed, but they are **not addressably** arrayed. As described in the specification addressably arrayed means that the cells are identifiable. Since, in the instantly claimed

method, each protein is produced and expressed separately and is then introduced into host cells, the identity of the encoded protein in the host cells is known. This means that in the instantly claimed method (1) it is not necessary to pick colonies; and to then (2) following screening, the selected proteins do not have to be sequenced to identify them or the hit positions.

(c) Individually screening each set of encoded proteins, whereby one or more proteins that have a predetermined property that differs from the target protein is/are identified, where all of the encoded proteins in each set have the same modification; and the proteins in each set differ from the proteins in another set by one amino acid and from the target protein by one amino acid.

As discussed, in the method of Giver *et al.* the modified proteins differ from the target protein by one or two amino acids. The instantly claimed methods require that the modified proteins differ by only a single amino acid.

(d) Individually screening each set of encoded proteins, whereby one or more proteins that have a predetermined property that differs from the target protein is/are identified so that is hits are identified.

By performing the method of Giver *et al.*, the colonies of cells are picked and screened, but the since they are not addressably arrayed, positives must be sequenced to identify them.

Hence, the method of Giver *et al.* is completely different from the instantly claimed methods of independent claims 1, 22-24, 27 and 30, as well as any dependent claims. Giver *et al.* fails to disclose elements of the claimed methods, including, but are limited to, one or more of: producing sets of nucleic acids in which each set encodes the same protein that differ from each other set by one amino acid, individually introducing each set of nucleic acids molecules into different host cells, addressably arraying host cells that include nucleic acids that express the same protein; separately expressing and screening each encoded protein. Thus, Giver *et al.* does not disclose all elements as claimed in any pending claim. Therefore, Giver *et al.* does not anticipate any pending claim, including rejected claims 1-6, 8-23, 30, 32, 33, and 42-44.

THE REJECTIONS OF CLAIMS 7, 24-29, 32, 33 UNDER 35 U.S.C. §103(a)

Several grounds of rejection are set forth under 35 U.S.C. §103(a) The particular grounds of rejection are discussed in turn below. As discussed below, neither Giver *et al.*

nor any reference of record, nor any combination of references, teaches or suggests steps (a) - (d) of the methods as outlined above and as recited in each of the independent claims. As discussed above, the method of Giver *et al.* necessarily produces a mixture of nucleic acid molecules and also of expressed proteins. Further Giver *et al.* introduces one to two mutations per molecule, not one as required by the instant claims. In the method of Giver *et al.* mixtures of nucleic acid molecules are introduced into cells, the cells are grown and colonies picked and screened. The polypeptides that are selected as having a property of interest must be sequenced to identify hit positions. Giver *et al.* does not teach a method in which cells are addressably arrayed, since the identify of the encoded protein in the picked colony is not known. The method of Giver *et al.* does not identify the protein and a hit position in a single step as in the instantly claimed methods.

None of the secondary references nor any reference of records provides any suggestion to change the operation of the method of Giver *et al.* nor any suggestion to modify the method, which relies on mixtures of primers to produce mixtures of nucleic acid molecules.

RELEVANT LAW

In order to set forth a prima facie case of obviousness under 35 U.S.C. § 103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used

against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Importantly, all claim limitations must be taught or suggested by the prior art to establish that claims are *prima facie* obvious. See, e.g., MPEP 2143.03 and In re Lowry, 32 F.3d 1579, 32 U.S.P.Q.2d 1031 (Fed. Cir. 1994), citing In re Gulack, 703 F.2d 1381, 217 U.S.P.Q. 401 (Fed. Cir. 1983), citing In re Royka, 490 F.2d 981, 180 U.S.P.Q.2d 580 (CCPA 1974).

The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); see, also, In re Papesh, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963). In addition, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

Rejection of claims 32 and 33

Claims 32 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giver *et al.* because "merely using a computer to automate a known process does not by itself impart nonobviousness to the invention. See Dann v. Johnston, 425 U.S. 219, 227-30, 189 USPQ 257, 261 (1976); In re Venner, 262 f.2d 91, 95,120 USPQ 193, 194 (EPA 1958)." The Examiner concludes that it, thus "would be obvious to one [ordinarily] skilled in the art to use a computer to automate the known processes disclosed by Giver *et al.* This rejection is respectfully traversed.

The rejected claims

Claim 32 is directed to the process of claim 1 that is automated; and claim 32 recites that it is computer-controlled.

Analysis

Giver *et al.*

As discussed above, Giver *et al.* does not teach or suggest a method that includes any or all of the steps (a)-(d) as follows:

(a) Producing a population of sets of nucleic acid molecules that encode modified forms of a target protein, where the members of each set encode the ***same*** modified protein,

and each encoded modified protein in a set differs from the encoded proteins in each other set and from the target protein by one amino acid

As discussed above, Giver *et al.* employs mixtures of oligonucleotides that in which **one to two** amino acids are modified in each encoded protein to produce mixtures of oligonucleotides.

(b) Individually introducing each set of nucleic acid molecules into host cells, and expressing the encoded protein, where the host cells are organized in an addressable array; the cells of each locus of the addressable array contain the same modified nucleic acid molecule; all proteins in each set contain the same modification; and the proteins in each set differ from the proteins in another set by one amino acid and from the target protein by one amino acid.

In the method of Giver *et al.* the mixtures of nucleic acid molecules are introduced into host cells and are expressed in the host cells. In the instantly claimed method, the same protein is expressed in each set of host cells. Further, in the method of Giver *et al.*, the cells may be arrayed, but they are **not addressably** arrayed. As described in the specification addressably arrayed means that the identity of the cells by virtue of the protein expressed is known. Since, in the instantly claimed method, each protein is produced and expressed separately and is then introduced into host cells, the identity of the encoded protein in the host cells is known. This means that (1) it is not necessary to pick colonies; and (2) following screening, the selected proteins do not have to be sequenced to identify them or the hit positions.

(c) Individually screening each set of encoded proteins, whereby one or more proteins that have a predetermined property that differs from the target protein is/are identified, where all of the encoded proteins in each set have the same modification; and the proteins in each set differ from the proteins in another set by one amino acid and from the target protein by one amino acid.

As discussed above, in the method of Giver *et al.* the proteins differ from the each other and the target protein by one or two amino acids. The proteins produced in the instant method differ by one amino acid, since one amino acid is modified at a time in each protein.

(d) Individually screening each set of encoded proteins, whereby one or more proteins that have a predetermined property that differs from the target protein is/are identified so that is hits are identified.

By performing the method of Giver *et al.*, the colonies of cells are picked and screened, but the since they are not addressably arrayed, positives must be sequenced to identify them.

Thus, Giver *et al.* fails to disclose elements of the claimed methods, including, but limited to, one or more of: producing sets of nucleic acids in which each set encodes the same protein that differ from each other set by one amino acid, individually introducing each set of nucleic acids molecules into different host cells, which are addressably arrayed, separately expressing and screening each encoded protein.

Conclusion

Whether or not automating the method with a computer confers unobviousness is not relevant, since as discussed and reiterative above, Giver *et al.* fails to teach or suggest numerous elements of the instantly claimed methods. There is nothing taught or suggested in Giver *et al.* that would have lead one of ordinary skill in the art to have modified the method of Giver *et al.* to produce any of the instantly claimed methods. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

The rejection of claims 7, 24 and 27-29

Claims 7, 24, and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giver *et al.* in view of Berlioz *et al.* (U.S. Patent No. 5,925,565) because, while Giver *et al.* allegedly only fails to teach using eukaryotic cells or assessing the titer of the viral vectors, Berlioz *et al.* teaches "assessing the titer of the viral vectors after transfection for each set of eukaryotic cells (column 14, lines 39-65) and where the viral vector encodes for a protein involved in viral replication (column 5, lines 35-65)." The Examiner concludes that it:

> would have been obvious at the time of the invention to combine the method taught by Berlioz et al. in Giver et al.'s method in order to study the effects of the protein in a eukaryotic setting. Berlioz et al. teaches a method that allows a eukaryotic cell such as a human cell to express a desired protein (column 6, lines 5-22) for the purpose of producing a therapeutic treatment (column 7, lines 15-25). Giver et al.'s method teaches screening for different proteins that exhibit the desired biological, chemical or physical properties (page 12810). The ability to manipulate these properties is important to create the desired therapeutic treatment. Thus one of ordinary skill in the art would be motivated to use Giver et al.'s method to design and screen for a desired product and use Berlioz et al.'s method to express the protein for screening or production of the product. Thus it would have been obvious to one of ordinary skill in the art to

combine the methods of Berlioz et al. [with those of Giver et al.].

This rejection respectfully is traversed.

Claims

Claim 7 is directed to the process of claim 1, where the nucleic acid molecules comprise viral vectors; and the cells are eukaryotic cells that are transduced with the vectors.

Independent claim 24 includes the method of claim 1 and recites that the nucleic acid molecules are in viral vectors and the titer of each set of vectors is assessed at step (b).

Claim 27 similarly recites that the nucleic acid molecules are in viral vectors and the titer of each set of vectors is assessed at step (b) and recites additional steps.

Analysis

As discussed above, the Giver *et al.* fails to disclose, teach or suggest teach any or all limitations of any of claims 1, 22-24, 27 and 30, and hence fails to disclose, teach or suggest any or all elements of the rejected dependent claims. Berlioz *et al.* fails to cure the deficiencies of Giver *et al.*, since Berlioz *et al.* does not teach or suggest a method that includes producing a population of sets of nucleic acid molecules that encode modified forms of a target protein, where all nucleic acid molecules in a set encode the same modified protein (step (a)); **addressably** arraying cells containing the nucleic acid molecules (step (b)), and/or individually screening each set of encoded proteins to identify one or more proteins that have a predetermined property that differs from the target protein is/are identified (step (d)). Therefore the combination of teachings of Giver *et al.* and Berlioz *et al.* does not result in the methods of claims 7, 24 and 27-29.

The rejection of claims 25 and 26

Claims 25 and 26 are rejected under 35 U.S.C. §103(a) as being unpatentable over Giver *et al.* further in view of Rivet *et al.* ((2000) Gene Therapy 7:924-929) because, Rivet *et al.* allegedly teaches real time virus titering (page 925) and using tagged replication and expression enhancement (page 926, right column), and hence cures the deficiencies in the teachings of Giver *et al.* and Berlioz *et al.*, which fail to teach real-time virus titering or tagged replication and expression enhancement.

The Examiner concludes that:

> [i]t would have been obvious to one of ordinary skill in the art to combine the methods of Giver *et al.*., Berlioz *et al.* and Rivet *et al.* in order to gain the benefit of determining the effectives of the viral vectors. Berlioz *et al.* teach that one his goals is to create a effective and stable viral vector (column 1,

> lines 10-17). Part of their method requires that they assess the titer of the viral vectors after transmission. Rivet *et al.'s* method provides further insight into the stability and efficacy of the vector by offering real time titering. Thus one or ordinary skill in the art would be motivated to combine the methods of Giver *et al.* and Berlioz *et al.* and Rivet *et al.* in order to gain the benefit of assessing the stability and efficacy of viral vectors more thoroughly.

This rejection respectfully is traversed.

Claims 25 and 26 are directed to the methods of claim 24, in which titering is effected by real time virus titering, As discussed above, Giver *et al.* fails to teach numerous elements of the independent claims, which Berlioz *et al.* fails to cure the deficiencies in the teachings of Giver *et al.* . Rivet *et al*, not only does not teach real time titering as claimed in claim 25 or claim 26, also does not cure the deficiencies in the teachings of Giver *et al.* and Berlioz *et al.* In particular, Rivet *et al.* does not teach a method that includes producing a population of sets of nucleic acid molecules that encode modified forms of a target protein, where all nucleic acid molecules in a set encode the same modified protein (step (a)); **addressably** arraying cells containing the nucleic acid molecules (step (b)), and/or individually screening each set of encoded proteins to identify one or more proteins that have a predetermined property that differs from the target protein is/are identified (step (d)). Hence, the combination of teachings of Giver *et al.*, Berlioz *et al.* and Rivet *et al.* does not result in the methods of claims 25 and 26. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

The rejection of claim 31

Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Giver *et al.* ((1988) *Proc. Natl. Acad. Sci. U.S.A. 95:* 12809-12813) in view of Persson *et al.* ((1985) *Journal of Virology 54*:92-97) because Persson *et al.* is alleged to teach a method that uses a Hill analysis for determining the rate in which host cells are infected with viruses (abstract, page 94, left column). The Examiner concludes that:

> [i]t would have been obvious to one of ordinary skill in the art to combine the methods of Giver *et al.* and Persson *et al.* to gain the benefit of deterring if the plasmids or vectors are infecting the host cells. Giver *et al.* teach a method that creates host cells of desired nucleic acids. In such a method, it would be desirable to know the rate of infection in order to determine how to structure an experiment (*e.g.* incubation times, concentration, etc.). Persson *et al.* provide such a method of determining the rate. Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the methods of Giver *et al.* and Persson *et al.* to gain the benefit of

determining the rate of infection of host cells.

This rejection respectfully is traversed.

Claim 31, which is dependent on claim 30, which includes the elements a)-d) as discussed above, and further includes recites that the "performance of the screened proteins is evaluated by a Hill analysis. As discussed above, Giver *et al.* fails to teach or suggest elements of the methods of the independent claim 30. As discussed above, Giver *et al.* does not teach or suggest a method that includes producing a population of sets of nucleic acid molecules that encode modified forms of a target protein, where all nucleic acid molecules in a set encode the same modified protein (step (a)); **addressably** arraying cells containing the nucleic acid molecules (step (b)) and/or individually screening each set of encoded proteins to identify one or more proteins that have a predetermined property that differs from the target protein is/are identified (step (d)). These elements are not taught or suggested by Persson *et al.* Therefore, the combination of teachings of Giver *et al.* and Persson *et al.* does not result in the method of claim 31. Therefore for these reasons and those discussed above, the Examiner has failed to set forth a *prima facie* case of obviousness of any of the pending claims.

* * *

In view of the above, reconsideration and allowance are respectfully requested

Respectfully submitted,

Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 17109-002001/911
Address all correspondence to:
Stephanie L. Seidman
Fish & Richardson P.C.
12390 El Camino Real
San Diego, California 92130
Telephone: (858) 678-5070
Facsimile: (202) 626-7796
email: seidman@fr.com